Chloroprene Background Information
EPA's Integrated Risk Information System (IRIS) Program

June 23, 2017

- Through the Integrated Risk Information System (IRIS) Program, EPA provides high quality, publicly available information on the toxicity of chemicals to which the public might be exposed. IRIS is the top tier source of toxicity information used by EPA to support environmental chemical risk management decisions– decisions that protect the public from cancer and other diseases.
- The IRIS assessment of chloroprene (2010) was developed following a very rigorous process (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1021).
    - The process began with the development of the assessment by a technically skilled, interdisciplinary scientific team comprised of Masters- and PhD-level biologists, toxicologists, epidemiologists, and statisticians within EPA. The team utilized EPA's long-standing risk assessment guidance to develop a complex hazard and dose-response assessment of chloroprene.
    - The process was completed following multiple reviews of the draft assessment including review by other scientists in EPA's program and regional offices, and by other Federal agencies and White House offices (e.g., NIEHS, OMB, CEQ). Subsequently, the draft assessment was made available for review and comment by the public and underwent independent, external peer review by a panel of scientific experts. Finally, the draft assessment was reviewed once again by EPA's program and regional offices, other Federal agencies, and White House offices.
- The IRIS assessment evaluated the published scientific evidence to develop both qualitative conclusions and quantitative analyses as part of the noncancer and cancer assessment for the inhalation route of exposure. The chloroprene assessment is a comprehensive, independent analysis that involved evaluation and integration of the available, relevant and reliable human, animal, and mechanistic evidence associated with chloroprene exposure.
    - The EPA toxicity assessment for chloroprene identifies 9 epidemiological studies with 8 cohorts (group of people that share a common characteristic or experience, e.g., work in the same area of an industry). Some studies may use the same cohorts but can be considered independently because they consider different parameters, e.g., cohorts may be followed for different amounts of time during the people's life.
    - Four epidemiologic studies detected statistically significant increases in liver cancers; increased risk of lung cancer was also observed, although few statistically significant associations were reported. Despite the various limitations in the epidemiologic database (e.g., healthy worker bias, potential co-exposure, and incomplete enumeration of cases), the associations detected in these studies add support to the cancer weight of evidence determination (see Sections 4.1.1.3 and 4.7.1.1 for more details).
    - There are many studies in animals, one of them being the National Toxicology Program (NTP) 2 year bioassay which is considered the gold standard of toxicity testing for noncancer and cancer effects. The NTP study (exposure concentrations of 12.8, 32, and 80 ppm [46.3, 155.8, and 289.6 mg/m^3]) includes noncancer and cancer toxicity data in male and female rats and mice, and a battery of genotoxicity tests that provide information on how a compound may cause cancer at the gene level.

- The IRIS assessment concludes that chloroprene is "likely to be carcinogenic to humans." This finding is based on consideration of the entire range of information which includes: some evidence of cancer in humans, strong evidence of multiple tumor types in multiple animals, and strong evidence that chloroprene interacts with DNA and causes cancer (see Sections 4.2.2 and 4.5.1 of the final chloroprene assessment: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1021tr.pdf).
    - The IRIS assessment for chloroprene provides a cancer narrative with compelling lines of evidence of a chemical likely to be carcinogenic to humans based on: 1) statistically significant and dose-related information from the chronic NTP bioassay showing the early appearance of tumors, development of malignant tumors, and the occurrence of multiple tumors within and across animal species; 2) evidence in humans of an association between liver cancer risk and occupational exposure to chloroprene; 3) suggestive evidence in humans of an association between lung cancer risk and occupational exposure; 4) proposed mutagenic action of chloroprene; and 5) structural similarities between chloroprene and the known human carcinogens, butadiene and vinyl chloride.
    - Specifically, in rats, increased incidences of neoplastic lesions primarily occurred in the oral cavity (both sexes), lung (males only), kidney (both sexes), and mammary gland (females). In mice, increased incidences in neoplasms occurred in the lungs (both sexes), circulatory system (all organs, both sexes), Harderian gland (both sexes), forestomach (both sexes), liver (females only), skin (females only), mammary gland (females only), and kidney (males only).
- The inhalation unit risk of 3×10^{-4} per $\mu g/m^3$ is based on the ***incidence of tumors in multiple organ systems in mice***, and represents a 95% upper confidence limit (see Table 1 below). The calculation of a composite cancer inhalation unit risk (IUR) is consistent with recommendations from the NRC (1994) for when multiple tumor types are identified, as is the case with chloroprene. The chloroprene toxicity assessment also concludes that there is strong evidence that chloroprene works via a mutagenic mode of action (i.e., works by damaging DNA directly) based on the following: 1) chloroprene is metabolized to an epoxide intermediate; 2) interaction with epoxide has been shown to cause DNA adducts (binds to DNA and this process could be the start of a cancerous cell); 3) chloroprene has been shown to cause mutations in bacterial cells; 4) similarities exist in tumor profile and sensitive species between chloroprene and butadiene, which is a known carcinogen; and 5) evidence of genetic alterations in chloroprene-induced lung tumors in rodents exists. **Because chloroprene was concluded to be mutagenic, EPA's 2005 Cancer Guidelines Supplemental document recommends the application of age-dependent adjustment factors (see calculation below). Thus, the adjusted IUR for chloroprene is 5×10^{-4} per ug/m^3.**

Table 1 – Dose-response modeling summary for female mouse tumors associated with inhalation exposure to chloroprene for 2 years.

Tumor Type[a]	Power Parameter c[b]	BMR	Point Of Departure[c]				Unit Risk[e] /(µg/m³)	Composite Unit Risk[f] /(µg/m³)
			Modeled from bioassay (ppm)		Continuous, Human equivalent[d] (µg/m³)			
			BMD	BMDL	BMD	BMDL		
Lung: alveolar/ bronchiolar adenoma or carcinoma	3.8	0.1	1.20	0.88	7.71×10^{2}	5.69×10^{2}	1.8×10^{-4}	2.7×10^{-4}
All organs: hemangio-sarcomas, hemangiomas[f,h]	5.9	0.1	10.1	5.75	6.52×10^{3}	3.71×10^{3}	2.7×10^{-5}	
All organs: hemangio-sarcomas, hemangiomas[g,i]	1.0	0.1	14.9	11.1	9.62×10^{3}	7.13×10^{3}	1.4×10^{-5}	
Mammary gland: carcinoma or adenoacanthoma	1.0	0.1	20.4	14.1	1.32×10^{4}	9.06×10^{3}	1.1×10^{-5}	
Forestomach: squamous cell papilloma or carcinoma	4.1	0.1	67.8	46.3	4.37×10^{4}	2.98×10^{4}	3.4×10^{-6}	
Liver: hepatocellular adenoma or carcinoma	4.2	0.1	4.24	2.45	2.73×10^{3}	1.58×10^{3}	6.3×10^{-5}	
Harderian gland: adenoma or carcinoma	2.9	0.1	27.1	12.6	1.75×10^{4}	8.13×10^{3}	1.2×10^{-5}	
Skin: sarcoma	1.6	0.1	9.49	7.18	6.11×10^{3}	4.63×10^{3}	2.2×10^{-5}	
Zymbal's gland: carcinoma	1.1	0.05	80.5	22.5	5.19×10^{4}	1.45×10^{4}	3.5×10^{-6}	

[a]Tumor incidence data from NTP (1998, 042076).
[b]Multistage-Weibull model: $P(d) = 1 - \exp[-(b_0 + b_1 d + b_2 d^2 + \ldots + b_k d^k) \times (t-t_0)^c]$, coefficients estimated in terms of ppm as administered in bioassay; lower stage b_i not listed were estimated to be zero. See Appendix C for modeling details.
[c]BMD = Concentration at specified extra risk (benchmark dose); BMDL = 95% lower bound on concentration at specified extra risk.
[d]Continuous equivalent estimated by multiplying exposures by (6 hours)/(24 hours) × (5 days)/(7 days).
[e]Unit risk estimated by dividing the BMR by the BMDL.
[f]Composite unit risk estimate, across all sites listed; see text for method.
[g]Highest exposure group dropped in order to better characterize low-dose responses.
[h]Treatment of early deaths (prior to final sacrifice) with hemangiosarcomas as fatal, with all other hemangiomas and hemangiosarcomas as incidental to death.
[i]All hemangiosarcomas (and hemangiomas) were considered incidental.

Application of Age-dependent adjustment factors

Risk for birth through <2 yr $= 3 \times 10^{-4}$ per $\mu g/m^3 \times 10 \times 2$ yr/70 yr $= 8.6 \times 10^{-5}$ per $\mu g/m^3$
Risk for ages 2 through <16 $= 3 \times 10^{-4}$ per $\mu g/m^3 \times 3 \times 14$ yr/70 yr $= 1.8 \times 10^{-4}$ per $\mu g/m^3$
Risk for ages 16 until 70 $= 3 \times 10^{-4}$ per $\mu g/m^3 \times 1 \times 54$ yr/70 yr $= 2.3 \times 10^{-4}$ per $\mu g/m^3$

To calculate the lifetime risk estimate for continuous exposure from birth for a population with default life expectancy of 70 years, the risk associated with each of the three relevant time periods is summed:

$$\text{Risk} = 8.6 \times 10^{-5} + 1.8 \times 10^{-4} + 2.3 \times 10^{-4} = 5.0 \times 10^{-4} \text{ per } \mu g/m^3$$

Using the above full lifetime unit risk estimate of 5×10^{-4} per $\mu g/m^3$ for continuous exposure from birth to 70 years, the lifetime chronic exposure level of chloroprene corresponding to an extra risk of 1×10^{-6} can be estimated as follows:

$$1 \times 10^{-6} \div 5 \times 10^{-4} \text{ per } \mu g/m^3 = 0.002 \ \mu g/m^3$$

Therefore, a risk of 1 in 10,000 would be associated with a lifetime exposure to 0.2 $\mu g/m^3$.

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